Effects of Mechanical Vibration on Relaxation and Diastolic Stiffness During Global Myocardial Ischemia in Isolated Canine Left Ventricle

博士論文

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（摘出犬左室標本における全体的心筋虚血中の弛緩及び拡張期弾性に及ぼす機械的振動の効果）

東北大学医学部付属病院第一内科

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Abstract

To examine whether mechanical vibration could release impaired relaxation and reduce the diastolic chamber stiffness under coronary ischemia, we used eight coronary-supported, isolated, isovolumetric canine left ventricular (LV) preparations. The coronary flow rate (CBF) was varied (100 %, 50 % and 25 % of the physiological value (90±10 ml/min/100 g LV weight)), and the pacing rate was changed 100, 140 and 180 bpm at each CBF level to impose a varying degree of impaired relaxation. The time constant of LV pressure fall (T) at an LV volume of 20 ml and chamber stiffness constant (K) from the diastolic pressure-volume relations were estimated at quiescent (i.e. no vibration applied) and under vibration. A mechanical 50 Hz, 2 mm-amplitude vibration was applied at diastole (i.e. from the time of (peak 20 % decrease of LV pressure) adjacent to the end-diastole). T increased significantly during ischemia at each heart rate (HR), but K showed no significant change during ischemia. In applying vibration, a shortening of T was observed under each condition, except at 100 bpm under control CBF. The shortening of T induced by mechanical vibration increased in magnitude at severe ischemia and it was dependent on the amplitude of the vibration. LV end-diastolic pressure and K decreased under vibration at higher HR (140 and 180 bpm) under ischemia. These results indicate that mechanical vibration at diastole releases impaired relaxation under coronary ischemia. Moreover, the vibration induces a reduction of diastolic LV chamber stiffness. Referring the results by Weisfeldt, we introduced the diastolic interval (DI)/T as a measure for quantitative estimation of incomplete

relaxation. DI/T decreased at higher HR in conditions of severe ischemia. The reduction in K by applying mechanical vibration was more prominent when DI/T was smaller than 3.5. The magnitude of the reduction in K correlated to DI/T ($r=-0.91$, $p<0.01$). Therefore, DI/T may be useful for estimating quantitatively the incompleteness of relaxation under ischemia and prospect the magnitude of reduction in K by mechanical vibration quantitatively.

Key words ; left ventricular diastolic properties, global ischemia, mechanical vibration, isolated heart

Running head: vibration on diastole under ischemia

Introduction

Impaired relaxation of the left ventricle (LV) has been reported to play an important role in the pathophysiology of various clinical situations such as angina pectoris, myocardial infarction, congestive heart failure, hypertrophic cardiomyopathy and dilated cardiomyopathy (1, 2). Palacious et al demonstrated that acute global ischemia impaired the myocardial relaxation process as a direct effect on the LV, not through change in load or contractility (3). One of the potential mechanisms for impaired relaxation during ischemia has been speculated that the sarcoplasmic reticulum takes up the cytosolic calcium more slowly due to an inadequate ATP supply (4), and a number of cross-bridges remained in an attached position during diastole.

On the other hand, it has been observed that a quick change of myofibrilar length decreased the force production at myosin cross-bridges (5). Koiwa et al showed that vibration applied throughout the whole cardiac cycle decreased LV systolic pressure in intact canine hearts (6). We hypothesized that an external mechanical vibration applied at diastole might release the impairment of relaxation through a direct effect on the presumably persisting cross-bridges. In the present study, this hypothesis was tested using isolated isovolumic canine LV under acute global ischemia.

Methods

Surgical procedure. Eight pairs of adult mongrel dogs were used. One of the pair was used as a source of isolated heart

(source dog, 10-16 kg in body weight) and another was used to support the coronary circulation of the isolated heart (support dog, 16-26 kg in body weight). The dogs were anesthetized with 25 mg/kg sodium pentobarbital. Then, the heart of the source dog was exposed via a bilateral thoracotomy under artificial ventilation with a volume ventilator (Model SN-480-4, Shinano Inc., Tokyo). After isolation of the heart, coronary perfusion of the isolated heart was maintained by cross-circulation through the extracorporeal coronary line, which consisted of a glass cannula inserted into the left main coronary artery, a roller pump (type SJ-1200, Mitsumi Scientific Ind Co., LTD., Tokyo), an air trap system in a warm water tank, a microfilter, a cannula inserted into a femoral artery of the support dog and a cannula inserted into the femoral veins of the support dog. We monitored the myocardial temperature by a needle thermister (Type MGA III-239, Nihon Kohden Co., LTD., Tokyo) throughout the experiment. Bilateral atria and the right ventricular free wall of the isolated heart were excised, and the edges were sutured by a silk thread to prevent bleeding. Mitral leaflets and chordae tendineae were cut and removed, and the mitral orifice was closed with a rigid rubber mitral plug equipped with a latex balloon. After a rough estimation of the weight of the isolated heart, the isolated LV was suspended on a firm supporting apparatus. The flat, disc-shaped tip of the vibrator (10 mm in its diameter) was attached perpendicularly to the LV anterior wall. A miniature acceleration sensor (EMIC 540M, Shin Nippon Sokki, Tokyo) was adhered to the shaft of the vibrator (Type 4809, Bruel & Kjaerum, Naerum, Denmark) to monitor the magnitude of input vibration and

this signl was amplified with a charge amplifier (Type 505 CAP Emic, Shin Nippon Sokki, Tokyo). LV pressure was measured with a micromanometer pressure transducer (PC370, Millar Instruments Inc., Houston, Texas) inserted into the LV through the mitral plug. Zero pressure was calibrated against a fluid-filled pressure transducer (P23XL, Spectramed Statham) through a stiff polyvinyl tube. Coronary perfusion pressure was also monitored with a fluid-filled pressure transducer. Epicardial pacing electrodes were sewn at the adjacent area of the atrio-ventricular junction. A bipolar surface electrocardiogram was recorded by silver electrodes sewn to the LV epicardial surface. After the completion of the preparations, LV was defibrillated and paced for 40 minutes for stabilization. PaO_2 and $PaCO_2$ of the support dog was maintained at physiological levels by controlling the ventilation and/or the oxygen inhalation and pH was corrected with 7 % sodium bicarbonate throughout experiment.

Input Vibration Control System. The vibration system is illustrated in outline in Figure 1. Briefly, a 50 Hz sine wave signal produced by a wide band function generator (Model FG-143, NF Circuit Design Block Co., LTD., Japan) was fed into the on-off circuit which determines the starting and end points of the vibration. The output signal from the on-off circuit was then lined to the DC power amplifier. The vibrator was driven by the DC power amplifier (type TI-2A, NEC San-Ei Co., LTD., Tokyo). To determine the starting and ending points of vibration, we manually controlled the timing by monitoring the high speed displasy of the signals in polygraph (Oscilloscope 2G66, NEC

San-Ei Co. LTD., Tokyo) at heart rate and coronary blood flow.

Experimental protocols and measurements. At first, coronary blood flow (CBF) was set at approximately 90 ml/min/100 g LV weight (control CBF), referring the value of the LV volume at initial rough estimation, and the pacing rate was fixed at 100 bpm. After stabilization period of 40 min, the pressure-volume curve was described continuously infusing the warmed water at an equivalent temperature (approximately 36 C) to the coronary blood by passing identical warmed water tank in the extra corporeal coronary circuit) into the LV (0.4 ml/sec) by a infusion pump (type SU-105, Erma Optical Works, Co. LTD.) until LV diastolic pressure reached 30 mmHg. We attached a linear displacement transducer to the syringe to measure the infused volume of the water. The vibration was restricted to the diastole in the cardiac cycle. That is, the mechanical vibration was applied from the time close to the peak LV pressure (peak 20 % decrease of the peak LVP) adjacent to the end-diastole. We increased the heart rate to 140 bpm and 180 bpm to change the extent of the relaxation (5), and repeated the same pressure-volume curve measurement at each heart rate. This pressure-volume curve was used to estimate the chamber stiffness.

After recording the pressure-volume curve, LV volume was fixed at 20 ml and the amplitude of diastolic vibration was changed from 1 mm to 2 mm and 3 mm at each heart rate. We caluculated the time constant of the LV pressure fall in each condition and estimated the effect of the magnitude of vibration.

To produce sever impaired relaxation, acute global ischemia was induced by reducing CBF from the control value to 50 % and 25

%. After a 15 minute stabilization period, the same mesurement was repeated.

To exclude the influence of hypothermia on relaxation and diastolic properties of the LV (7,8), myocardial temperature was carefully maintained at 36±1°C.

The electrocardiogram, LV pressure measured by both catheter tipped micromanometer and fluid filled catheter transducer system, input vibration signal and volume signal were recorded on an analog tape recorder (type KS-616, Sony Magnescale, Tokyo) and a thermal direct printer (Omnicorder 8M15, NEC San-Ei Co., LTD., Tokyo). The pressure-volume curve was recorded on an X-Y recorder (CX-446, Ono Sokki Co. LTD., Tokyo) at an X-axis gain of 1 ml/0.5 cm and a Y-axis gain of 1 mmHg/2.5 mm.

Data analysis

Time constant of the LV pressure fall (T). Using a signal precessor (7T17, NEC San-Ei Co. LTD., Tokyo), LV pressure was digitized at a constant rate of 2 KHz and fitted to function 1 using the method of least squares as described by Weiss et al (9).

$$P = Po \times e^{-t/T} \qquad 1)$$

P; instantaneous LV pressure

Po; LV pressure at peak negative dp/dt

t; instantaneous time

T; time constant of LV pressure fall

T characterizes the rate of the LV relaxation and has been reported to be a relatively load independent measure (10). This computation was performed from peak negative dp/dt to the time

when the pressure decreased to a level 5 mmHg higher than LV end-diastolic pressure (LVEDP).

No quantitative index of incomplete relaxation has been reported. Therefore, we introduced the diastolic interval (DI)/T as a quantitative index for incomplete relaxation, extending the results by Weisfeldt et al (22). Here, the diastolic interval was defined as the period from the peak negative dp/dt to the end-diastole. This index was used in the present study to estimate the effect of the mechanical vibration on the chamber stiffness either at each pacing rate or at each CBF.

Chamber stiffness constant of the LV at diastole (K). The LV diastolic chamber stiffness was measured using the method by Diamond et al (10), as follows.

$$P = xe^{KV - C/K} \qquad 2)$$

P; LV pressure (mmHg)

V; intraventricular volume (ml)

K; constant (1/ml)

c; constant (mmHg/ml)

x; constant

One can obtain the following equation by differentiation.

$$dP/dV = KP + C \qquad 3)$$

K is a stiffness constant of the LV which is independent of both pressure and volume. Diastolic pressure-volume curves between 5 mmHg and 25 mmHg were used for curve fitting to calculate K by computer (PC9801M2, NEC Co., LTD., Tokyo) and digitizer (type KP4030B, Graphtec Co., LTD., Tokyo).

Statistics. In analysis, all extrasystolic beats and postextrasystolic beats were excluded. Data were compared using

a paired t test. Differences were considered to be stastically significant at $p<0.05$. All values were expressed as means$\pm$SEM.

Results

Time constant of the LV pressure fall (T). T at 50 % CBF compaired to those at control increased significantly at each heart rate (73.0$\pm$12.3 vs 104.6$\pm$18.2 ms, 59.1$\pm$5.2 vs 84.7$\pm$9.7 ms and 43.2$\pm$4.6 vs 65.2$\pm$5.1 ms at a pacing rate of 100, 140 and 180 bpm respectively, all $p<0.05$). T under 25 % of CBF further increased compared to those under 50 % CBF (140 bpm; 152.3$\pm$21.3 ms, $p<0.05$ and 180 bpm; 138.3$\pm$19.9 ms, $p<0.01$). T decreased with an increment in heart rate, from 100 bpm to 180 bpm at each level of CBF.

Figure 2 shows the actual trend of LV pressure at 140 bpm under 25 % CBF. The rate of LV pressure fall was accelerated by applying mechanical vibration. Moreover, a decrease in LVEDP was noted under vibration.

Figure 3 shows the superposition of LV pressure at quiescent and under vibration. LV pressure fall (control CBF; top, 25 % CBF; bottom) became more rapid by applying vibration both at control and under 25 % CBF. Moreover, LVEDP decreased under vibration when CBF decreased to 25 %.

The effect of vibration on T is summarized in Table 1. T values are expressed as percent (% T) to those at control at each heart rate. T decreased significantly by vibration, except at control CBF and a heart rate of 100 bpm.

The difference of T between at quiescent and under vibration increased as CBF reduced at each heart rate.

The effect of the amplitude of vibration on T is shown in Table 2. The decrease in T (%) showed amplitude dependency at 25 % CBF. At 100 % or 50 % CBF, decrease in T tended to increase as a magnitude of vibration became greater, but the increase was not significant.

DI/T at quiescent condition decreased significantly with reduction in CBF at each heart rate (Table 3). DI/T increased under vibration, except at heart rate of 100 and 180 bpm under control CBF.

Diastolic pressure-volume relationship. Figure 4 illustrates actual trends of the diastolic pressure-volume relation at 140 bpm under 25 % CBF. Vibration shifted the diastolic pressure-volume relation to the right lower in this figure.

LVEDP at higher volume tended to increase as the ischemia became severe, but this increase was not significant.

Figure 5 shows the decrease in LVEDP by applying mechanical vibration. Decrease in LVEDP was greater at larger LV volume and under much severe ischemia.

Diastolic LV chamber stiffness constant (K). K tended to increase as CBF reduced, but not significantly (Table 4). Vibration significantly decreased K under 50 % CBF at 180 bpm and 140 bpm and under 25 % CBF. T correlated with K significantly ($r=0.76$, $p<0.01$). Figure 6 shows the relationship between DI/T and K. Closed circles and open circles represent values at quiescent and under vibration, respectively. DI/T inversely correlated with K significantly ($r=-0.88$, $p<0.01$). The

magnitude of reduction in K correlated to DI/T ($r=-0.91$, $p<0.01$).

Discussion

In clinical setting, the significance of impaired relaxation, especially of ischemic heart disease, has been emphasized by several investigators (4, 11, 12). Recently, a couple of drugs has been reported to improve diastolic function and to be avalable for the management of patients with congestive heart failure and/or ischemic heart disease (13, 14). In this study, we examined whether the mechanical vibration could be a tool, in future, to improve the diastolic abnormality in the ischemic heart using cross-circulated, isolated isovolumic canine LV preparations. Time constant of LV pressure fall increased at acute global ischemia as reported in previous studies (3). In applying mechanical vibration to LV diastole, it exerts instantaneous effect on the diastolic mehcanical properties of the ventricle. That is, the vibration instantaneously increase the rate of LV pressure fall under ischemia and simultaneously decreases abnormally elevated LV stiffness even though it was not sufficient to revert completely to the control value.

Mechanism of improvement of relaxation by vibration. In the process of relaxation, calcium is released from the calcium-troponin complex to cytoplasm and uptaken into sarcoplasmic reticulum by ATPase. This process has been reported to be c-AMP dependent (12) and energy consuming process. During this process, detachment of myosin cross-bridges results in a decline

in tension. Impairment of cross-bridge detachment plays an important role in impaired relaxation of the ventricle (15). Actually, impaired relaxation associated with ischemia has been reported to occur under various conditions such as an ATP-deficiency, cytosolic calcium overload, decreased c-AMP and decreased ATPase activity of the sarcoplasmic reticulum (7).

In applying the vibration (Figure 2), time constant of relaxation (T) was decreased, and it again increased to the level at quiescent condition immediately after a cessation of vibration. This change in relaxation, therefore, seems to reflect the direct action of the vibration on the myocardial contractile proteins rather than the relatively gradual reaction through the metabolic changes such as an improvement of coronary perfusion, the change in ATP level or c-AMP concentration. However, we could not neglect the possibility that the vibration abruptly reduces the cytosolic calcium concentration and accelerates the dissociation of calcium from the troponin C, or changes the affinity of troponin C for calcium (16). Under ischemic condition, the cytosolic calcium concentration has been reported to be higher even at relaxation phase (17).

Several investigators have observed a decline of active tension or pressure by minute vibration which was externally applied throughout the cardiac cycle in isolated (18, 19) and intact (6) experimental preparations and human LV (20). When mechanical vibration was applied during the whole cardiac cycle in in-situ ventricle, instantaneous drop in LV systolic pressure, stroke volume, aortic pressure was induced with no significant changes in heart rate, systemic vascular resistance or LVEDP.

The magnitude of vibration-induced depression in myocardial function has been demonstrated to be dependent on the input energy ($\propto (\text{Amplitude})^2 \times (\text{frequency})^2$) (6, 18) and basal myocardial contractility. Koiwa et al (6) speculated that these effects were not induced through the change of neurohumoral control, but might be related to the mechanical effect to myosin cross-bridges. Huxley et al (5) reported that quick change in the muscle fiber length (approximately 1% of half sarcomere length) reduced the number of force-generating cross-bridges and caused a change in tension due to decrease of the number of cross-bridges. Koiwa et al demonstrated that applying vibration of 56 Hz, the arrested isovolumic LV (60 mmHg of LV pressure) vibrated as mode 2 behavior in stroboscopically illuminated slow-motion images (21). The mode 2 vibration means that the whole ventricular wall vibrates as the bending motion with four nodal lines from the apex to the base. If we assume the LV as the thin walled ellipse without change of volume during vibration, these vibration would produce approximately 0.5 % change of LV circumferential fiber length when vibration of 50 Hz and 3 mm in magnitude was applied. We are now speculating that these small change of fiber length might cause a sudden change in tension by the same effect as reported by Huxley et al.

Abrupt increase in load at late portion of contraction of the cardiac muscle causes a premature onset and more rapid rate of relaxation. Brusaert et al termed this phenomenon "load dependence of relaxation" (15). Load dependence of relaxation has been observed in mammalian myocardium and not observed in

frog myocardium with little function of sarcoplasmic reticulum,and was suppressed by caffein and hypoxia. Therefore, load dependence of relaxation has been considered to require the presence of calcium-sequestering membrane. Ariel et al (22) reported that, in intact canine heart, the quick stretch (pulse-like volume increment of 6 ml blood) of LV chamber just after the peak pressure in a non-ejecting LV produced a more rapid rate of LV pressure decay. They explained this phenomenon by the concept of "load dependence of relaxation" reported by Burtsaert et al (15). They speculated that if a load of over bearing capacity was applied to cardiac musle, the muscle would begin to lengthen. The results in the present study looks like as if it were analogous to those of above-mentioned reports. However, essentially different phenomenon are observed in this study compared to those by Brusaert et al. That is, ischemia has been considered to depress the function of sarcoplasmic reticulum due to inadequate supply of ATP. Therefore, if the mechanism described by Brusaert et al works in our study, the vibration or the pulse at early diastole should be <u>less</u> load-dependent. This is sharp contrast in our study of imposing ischemia. We observed that the mechanical vibration increased the rate of relaxation in the ventricle under ischemia. The effects of vibration on relaxation would be hard to explain soly by the "load dependence of relaxation".

Another factor inducing impaired relaxation has been reported as non-uniformity of LV relaxation (15). We might be able to neglect the spatial non-uniformity among each coronary perfused area, because global ischemia was imposed in this study. However, it might be able to speculate that the transmural non-

uniformity could be existed when global ischemia was imposed. That is, under ischemia, subendocardial layer suffers much serious ischemia than subepicardial layer, and relaxation of subendocardial layer would be impaired more severely than that of subepicardial layer. Mechanical vibration might be able to release these transmural non-uniformity and eventually might also be able to improve LV diastolic properties.

Effects of vibration on LV chamber stiffness LV chamber stiffness is determined by extrinsic and intrinsic factors (12). The isolated LV preparation in this study essentially abolished extrinsic factors and the intrinsic factors should be considered in interpreting the results of this study.

In the present study, significant decrease in coronary perfusion pressure was not caused by mechanical vibration. Therefore, dilatation of the coronary vasculature due to relaxation of vascular smooth muscle by vibration seems not to contribute to a decrease of diastolic LV stiffness; i.e., the contribution of "erectile effect" would be negligible (23).

Accordingly, the most probable factor which was responsible for decrease in LV chamber stiffness under the vibration would be the decrease of active series elasticity of the LV wall. That is, decrease in the LV chamber stiffness under vibration would be induced by the reduction in incomplete relaxation which has been considered to be the effect of the residual cross-bridge (4). When the LV relaxed sufficiently at end-diastole, vibration would not influence LVEDP or LV stiffness even if vibration increased the rate of relaxation as shown in Figure 3 and Figure 6. In

contrast, when LVEDP or LV stiffness was increased due to the impairment of rate and extent of relaxation, vibration would release impaired relaxation, lower the LVEDP and reduce LV stiffness.

Relation between incomplete relaxation and increased K.

Weisfeldt et al showed that, in non-ischemic intact heart, incomplete relaxation was possible under tachycardia of more than 170 bpm or after administration of propranolol (24). They concluded that an interval shorter than 3.5T between peak negative dp/dt and end-diastole strongly suggested the presence of incomplete relaxation, and its effect on an increasing ventricular stiffness. However, it still remains to be determined if the 3.5T could be used under ischemic condition to predict the presence of incomplete relaxation. At present, we cannot find any quantitative index to estimate the incompleteness of relaxation. Therefore, DI/T was introduced as a quantitative index of the incomplete relaxation extending the results by Weisfeldt et al in the present study. Serizawa et al (25) reported linear relationship between T and LVEDP in an experiment using isolated isovolumic rabbit heart under hypoxia, and speculated the positive relationship between impaired relaxation and increased LV stiffness, even they did not measure the stiffness directly. In this study, we observed a direct correlation between T and the LV stiffness (K) ($r=0.76$, $p<0.01$) under ischemia. Moreover, modification of T by adding the factor of diastolic interval (DI/T) showed better correlation coeficient ($r=0.88$, $p<0.01$) than utilizing T to the chamber stiffness (Figure 6). This relationship between DI/T and K fitted better

by an exponential curve ($r=0.906$, $p<0.01$) than by a linear correlation, suggesting much important role of the impaired relaxation on the increased stiffness at smaller DI/T. Vibration significantly decreased K when DI/T was less than 3.5. In other words, incomplete relaxation would play an important role on an increase in K at quiescent condition when this index was less than 3.5. The result that magnitude of reduction in K correlated to DI/T ($r=-0.91$, $p<0.01$) suggests that vibration are much more effective when DI/T is reduced by severe ischemia and/or tachycardia. These results indicate that it would be possible to estimate its pathophysiological importance of LV incomplete relaxation on the abnormally elevated LVEDP or K and predict the magnitude of improvement by applying mechanical intervention using this index of DI/T.

Limitation of this study. The model used in the present study was an acute global ischemia of normal canine myocardium. This differed from the more complex clinical situation observed in patients with coronary artery disease involving fibrosis and regional ischemia. Vibration may not reduce LV chamber stiffness based on the histological change such as intramyocardial edema. Moreover, in chronic ischemic heart disease or dilated cardiomyopathy with fibrosis or inhomogeneity of the myocardium (2), vibration may not improve diastolic dysfunction. Concerning these points, further study is necessary.

In summary, the present study indicated that mechanical vibration applied at diastole released impaired relaxation of the LV under acute ischemia. The results demonstrated the presence

of the incomplete relaxation under global ischemia and revealed the close relationship between the incomplete relaxation and increased stiffness of the LV. These effects of vibration were dependent on the magnitude of vibration and the mechanisms involved were speculated to be related to the direct action to force-generating cross-bridges throughout the diastole.

References

1. Hirota Y: A clinical study of left ventricular relaxation. Circulation 1980;62:756-763
2. Bortone AS, Hess OM, Chiddo A, Ganlione A, Locuratolo N Caruso G and Rizzon P: Functional and structural abnormalities in patients with dilated cardiomyopathy. J Am Col Cardiol 1989;14:613-23
3. Paracious I, Newell JB and Powell Jr WJ: Effects of acute global ischemia on diastolic relaxation in canine hearts. Am J Physiol 1978;235:H720-H727
4. Gilbert JC and Glantz SA: Determinations of left ventricular filling and of the diastolic pressure-volume relation. Circulation Research 64: 827-857, 1989
5. Huxley AF and Simmons RM. Proposed mechanism of force generation in striated muscle. Nature 1970;233:533-538
6. Koiwa Y, Hoshi N, Ohyama T, Takagi T, Kikuchi J, Honda H and Takishima T: The response of normal and failing heart to externally applied vibration in the canine open chest preparation. Tohoku J Exp Med 1989;157:183-184
7. Parmley WW and Sonnenblick EE: Relaxation between mechanics of contraction and relaxation in mammalian cardiac muscle. Am J Physiol 1969;216(5):1084-1091
8. Templeton GH, Wilderthal K, Willerson JT and Reardon WC: Influence of temperature on the mechanical properties of cardiac muscle. Circ Res 1974;34:624-634
9. Weiss JL, Frederiksen JW and Weisfeldt ML: Hemodynamic determinamnts of time-course of fall in canine left

ventricular pressure. J Clin Invest 1976;58:751-760

10. Diamond G, Forrester JS, Hargis J, Parmley WW, Danzig R and Swan HJC: Diastolic pressure-volume relationship in the canine left ventricle. Circulation Research 1971;29:267-275
11. Mann T, Goldberg S, Mudge Jr GH and Grossman W: Factors contributing to altered left ventricular diastolic properties during angina pectoris. Circulation 1979;59:14-20
12. Grossman W, McLaurin L and Hill C: Diastolic properties of the left ventricle. Ann Int Med 1976;84:316-326
13. Carroll JD, Lang RM, Neumann AL, Borow KM and Rajfer SI: The differential effects of positive inotropic and vasodilator therapy on diastolic properties in patients with congestive cardiomyopathy. Circulation 1985;74:815-825
14. Monrad ES, McKay RG, Baim DS, Colucci WS, Fifer MA, Heller GV, Royal HD and Grossmann W: Improvement in indexs of diastolic performance in patients with congestive heart failure treated with milrinon. Circulation 1984;70:1030-1037
15. Burtsaert DL, Housmans PR and Goethals: Dual control of relaxation its role in the ventricular function in mammalian heart. Circ Res 1980;47: 637-652
16. Lakatta EG: Starling's law of the heart is explained by an intimate interaction of muscle length and myofilament calcium activation. J Am Coll Cardiol 1987;10:1157-1164
17. Kihara Y, Grossman W and Morgan JP: Direct measurement of changes in intracellular calcium transients during hypoxia, ischemia, and reperfusion of the intact mammalian heart. Circulation 1989;65:1029-1044

18. Vukas M, Malek I and Hjalmarson AC: Myocardial depressant effect of vibrations in isolated rabbit heart. Scand J Clin Invst 1978;38:421-424

19. Koiwa Y, Hoshi N, Ohyma T, Takagi T, Kikuchi J, Honda H and Takishima T: Effect of left ventricular volume on the magnitude of functional depression by external minute vibration. Tohoku J Exp Med 1989;159:167-168

20. Koiwa Y, Ohyama T, Takagi T, Kikuchi J, Honda H, Hoshi N and Takishima T: Clinical demonstration of vibration-induced de pression of left ventricular function. Tohoku J Exp Med 1989;159:247-248

21. Koiwa Y, Ohyama T, Takagi T, Kikuchi J, Honda H, Hashiguchi R, Shimizu Y, Butler JP and Takishima T: The left ventricular vibration mode in the ventricular transfer function method and at the moment of the first heart sound. Frontiers Med Biol Engng 1988;1:59-70

22. Ariel Y, Gaasch WH, Bogen DK and McMahon TA: Load-dependent relaxation with late systolic volume steps: servo-pump studies in the intact canine heart. Circulation 1987;75:1287-1294

23. Vogel WM, Apstein CS, Briggs LL, Gaasch WH and Ahn J: Acute alterations in left ventricular diastolic chamber stiffness role of the "Erectile" effect of coronary arterial pressure and flow in normal and damaged heart. Circ Res 1982;51:465-478

24. Weisfeldt ML, Frederiksen JW, Yin FCP and Weiss JL: Evidence of incomplete left ventricular relaxation in the dog prediction from the time constant for isovolumic pressure

fall. J Clin Invest 1978;62:1296-1302

25. Serizawa T, Vogel WM, Apstein CS and Grossman W: Comparison of acute alteration in left ventricular relaxation and diastolic chamber stiffness induced by hypoxia and ischemia. J Clin Invest 1981;68:91-102

Table 1. coronary blood flow and time constant at each heart rate at quiescent condition and under vibration

	control CBF		50% CBF		25% CBF	
%T at HR100						
vibration (-)	100.0±0.0	NS	143.0± 3.6	p<0.05	257.1±17.5	p<0.05
vibration (+)	90.2±4.9		111.4± 5.9		208.1± 7.6	
△ %T	9.9±4.9		31.7± 5.6	*	49.0±10.7	*
%T at HR140						
vibration (-)	100.0±0.0	p<0.05	142.4± 7.8	p<0.01	245.6±20.9	p<0.01
vibration (+)	90.4±2.4		118.4± 7.3		214.8±20.3	
△ %T	9.6±2.4		24.0± 3.4	*	30.8± 4.0	*
%T at HR180						
vibration (-)	100.0±0.0	p<0.05	153.7±10.3	p<0.01	341.1±74.6	p<0.05
vibration (+)	93.1±1.9		130.1± 9.0		289.1±69.2	
△ %T	6.9±1.9		23.6± 3.0	**	52.0±13.1	*

%T is the T value relative to T at control coronary blood flow (CBF). △%T is difference between %T at quiescent conditionand %T under vibration. HR, heart rate. *, p<0.05; **, p<0.01 control CBF vs 50% CBF or 25% CBF.

Table 2. Relation between improvement (%) of T and magnitude of input vibration at HR 100

	magnitude of input vibration		
	1 mm	2 mm	3 mm
control CBF	5.5±2.7	9.9±4.9	11.1±9.4
50% CBF	9.0±1.7	22.1±3.7 *	27.2±4.9 *
25% CBF	6.8±1.6	18.6±2.7 **	28.4±4.9 *†

Improvement (%) of T is calculated as (1 - T under vibration/ T at quiescent condition)x100. *, $p<0.05$; **, $p<0.01$ 1 mm vs 2 mm or 3 mm. †, $p<0.05$ 2 mm vs 3 mm.

Table 3. Diastolic interval/time constant at quiescent condition and under vibration

	control CBF	50% CBF	25% CBF
HR 100			
vibration (-)	5.31±0.61	3.99±0.55 **	2.16±0.38 ** ††
vibration (+)	5.97±0.44 NS	5.12±0.79 p<0.05	2.68±0.39 p<0.01
HR 140			
vibration (-)	3.83±0.23	2.83±0.35 **	1.67±0.25 ** ††
vibration (+)	4.34±0.32 p<0.05	3.58±0.47 p<0.05	1.94±0.29 p<0.05
HR 180			
vibration (-)	3.19±0.20	2.31±0.08 *	1.33±0.30 * †
vibration (+)	3.48±0.22 NS	2.98±0.13 p<0.01	1.65±0.29 p<0.05

*, p<0.05; **, p<0.01 control CBF vs 50% CBF or 25% CBF. † , p<0.05; †† , p<0.01 50% CBF vs 25% CBF.

Table 4. Diastolic chamber stiffness constant (K) (1/ml)

	control CBF	50% CBF	25% CBF
HR 100			
vibration (-)	0.0551±0.0111	0.0580±0.0095	0.0753±0.0068
vibration (+)	0.0542±0.0123	0.0575±0.0115	0.0671±0.0102 *
HR 140			
vibration (-)	0.0575±0.0129	0.0612±0.0104	0.0767±0.0091
vibration (+)	0.0564±0.0127	0.0569±0.0099 *	0.0681±0.0077 *
HR 180			
vibration (-)	0.0644±0.0145	0.0670±0.0095	0.0777±0.0079
vibration (+)	0.0617±0.0157	0.0627±0.0098 *	0.0682±0.0082 **

*, $p<0.05$; **, $p<0.01$ vivration (-) vs vibration (+)

Figure legends

Figure 1: Experimental set up.

Figure 2: Change in left ventricular pressure under the vibration applied at diastole, in the condition at a heart rate of 140 bpm and 25% coronary blood flow. The rate of relaxation became rapid immediately after applying vibration and LVEDP was reduced. After cessation of vibration, the rate of relaxation and LVEDP returned to pre-vibration level within a beat.

Figure 3: Superposition of the left ventricular (LV) pressure at quiescent; vibration (-) and under vibration; vibration (+). Upper panel shows LV pressure at control coronary blood flow (CBF). Lower panel shows LV pressure under 25 % CBF. Applying vibration, LV pressure at both level of CBF shows instantaneous acceleration of pressure fall. At end-diastole, LV pressure at control CBF showed no change under vibration. However, LV end-diastolic pressure at 25 % CBF decreased under vibration.

Figure 4: An example of superposition of diastolic pressure-volume relation at a heart rate of 140 bpm under 25% coronary blood flow at quiescent and under vibration.

Figure 5: Changes in left ventricular end-diastolic pressure (LVEDP) under vibration at 100 %, 50% and 25% coronary blood flow (CBF) at each heart rate. ● , control CBF; ▲ , 50% CBF; ■ , 25% CBF. *, $p<0.05$; **, $p<0.01$ LVEDP at quiescent vs LVEDP under vibration.

Figure 6: Relationship between diastolic inteval (DI)/T and K at quiescent (closed circle; ●) and under vibration (open circle; o). DI/T was inversely correlated linearly with the K ($r=-0.88$, $p<0.01$). Values are mean at each heart rate and each level of coronary blood flow.

Figure 1

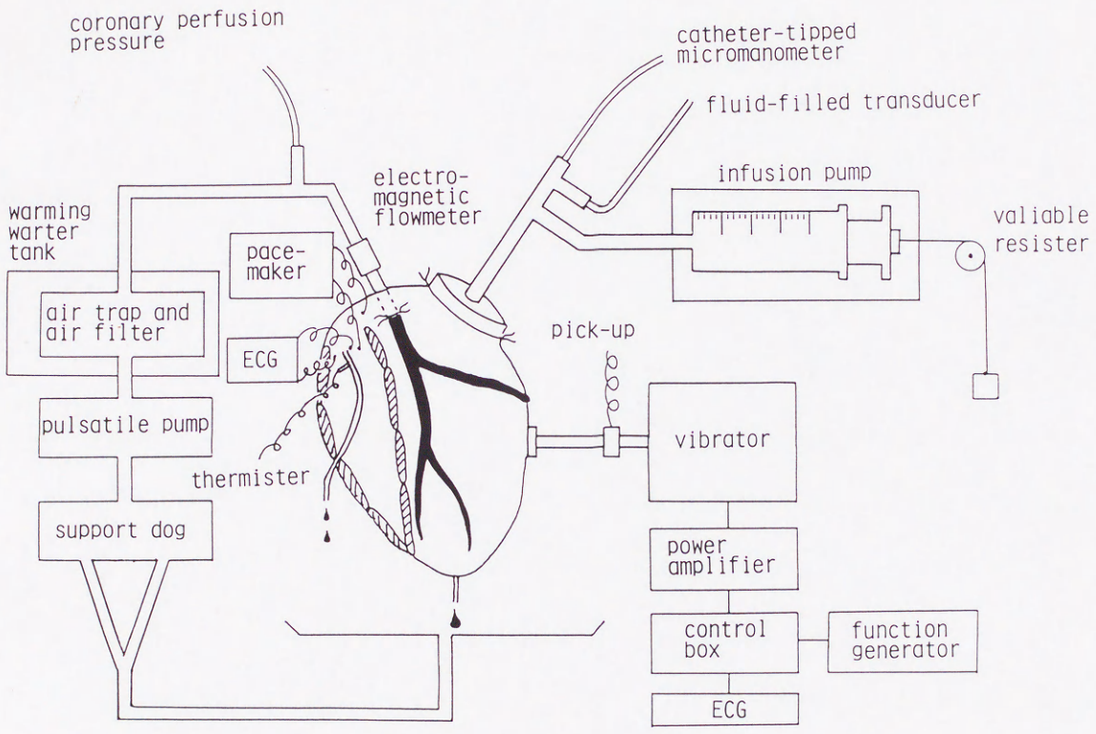

coronary perfusion pressure
catheter-tipped micromanometer
fluid-filled transducer
electro-magnetic flowmeter
infusion pump
warming warter tank
pace-maker
valiable resister
air trap and air filter
ECG
pick-up
pulsatile pump
vibrator
thermister
support dog
power amplifier
control box
function generator
ECG

Figure 2

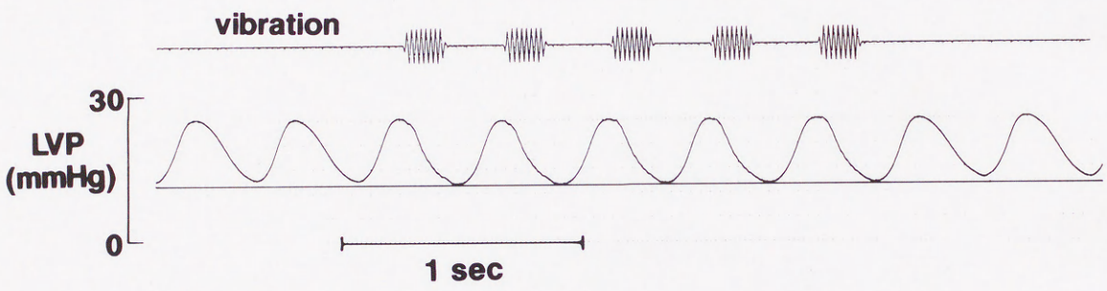


Figure 3

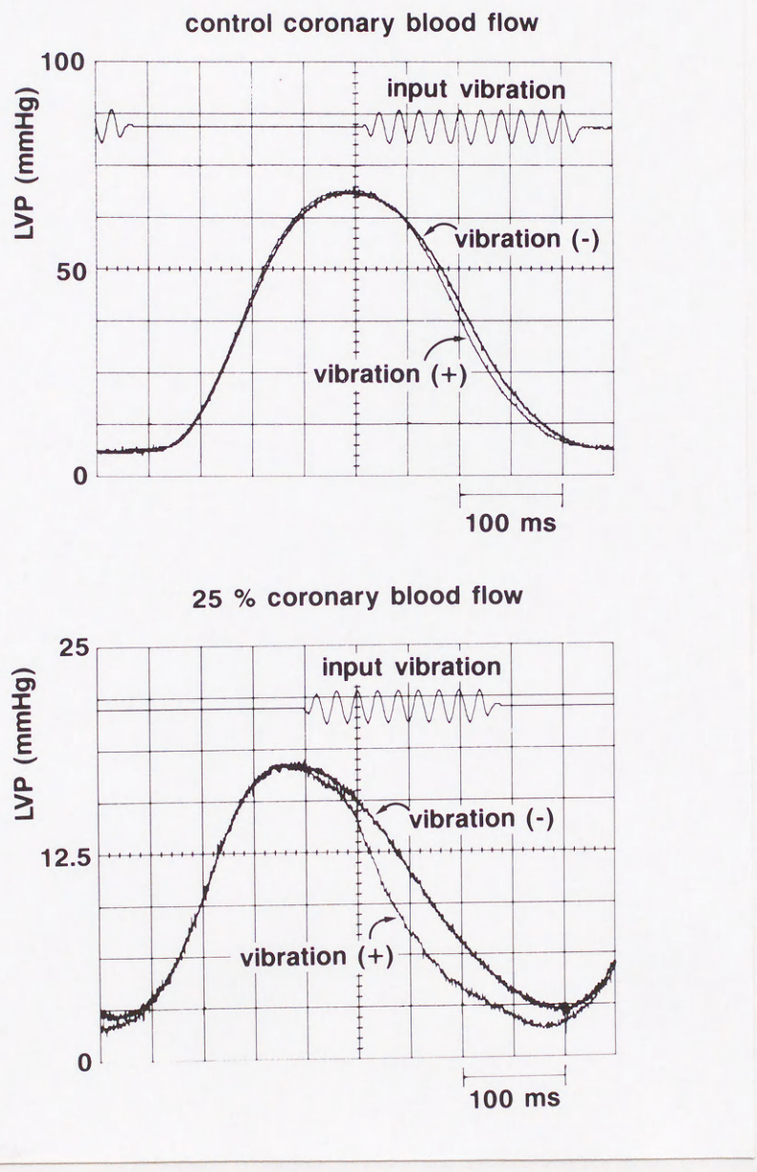

control coronary blood flow
100
50
0
LVP (mmHg)
input vibration
vibration (-)
vibration (+)
100 ms
25 % coronary blood flow
25
12.5
0
LVP (mmHg)
input vibration
vibration (-)
vibration (+)
100 ms

Figure 4

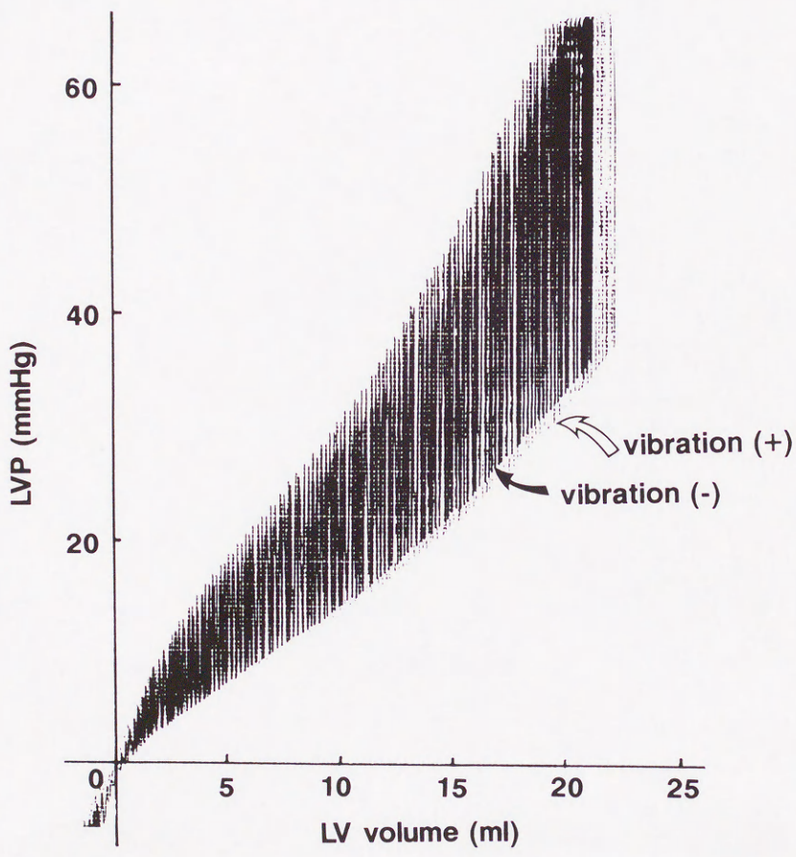

60
40
20
0
LVP (mmHg)
5
10
15
20
25
LV volume (ml)
vibration (+)
vibration (-)

Figure 5

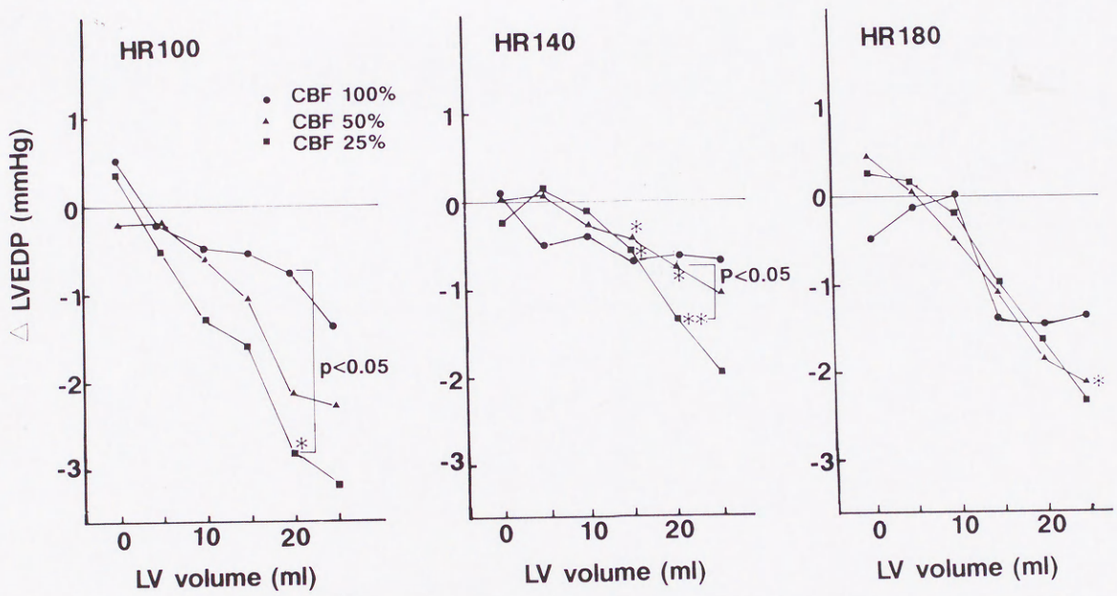
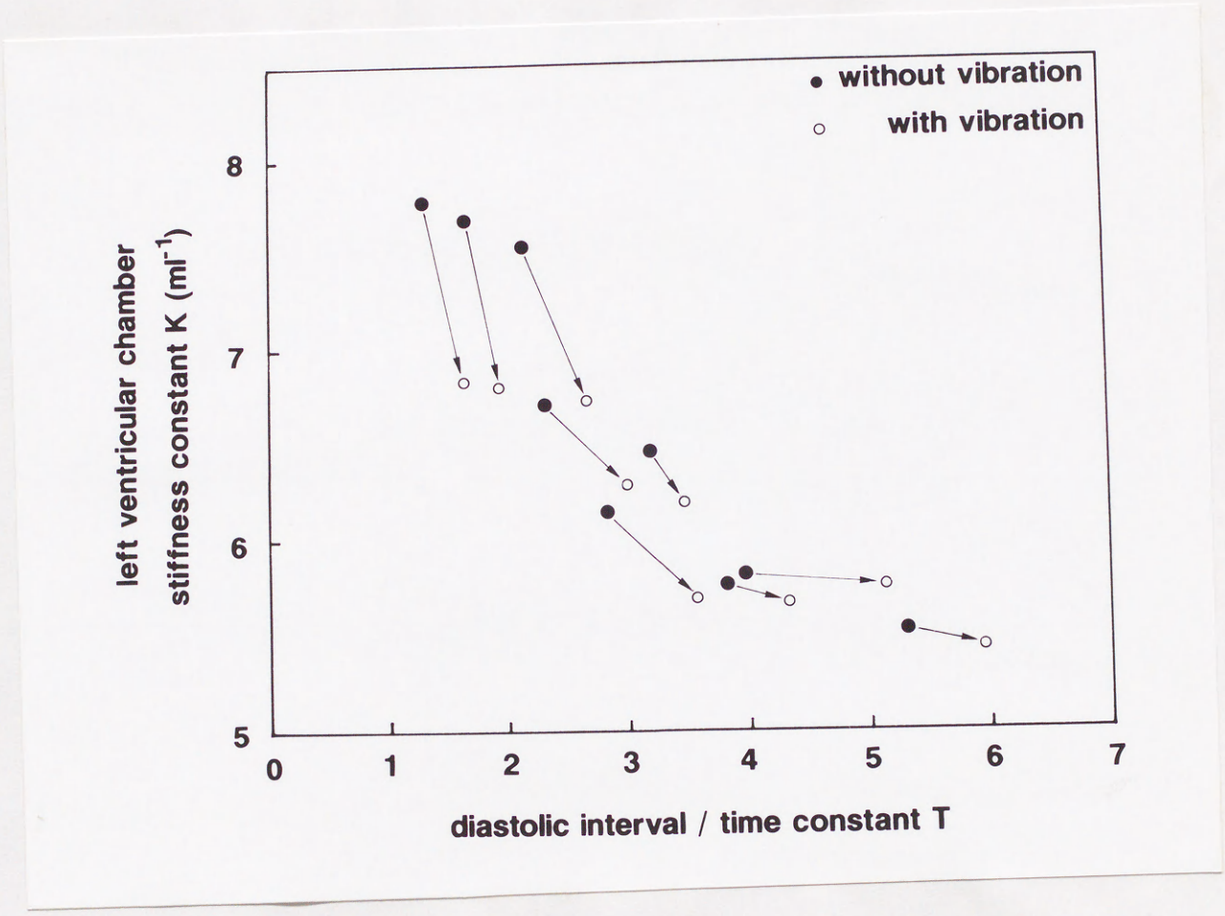
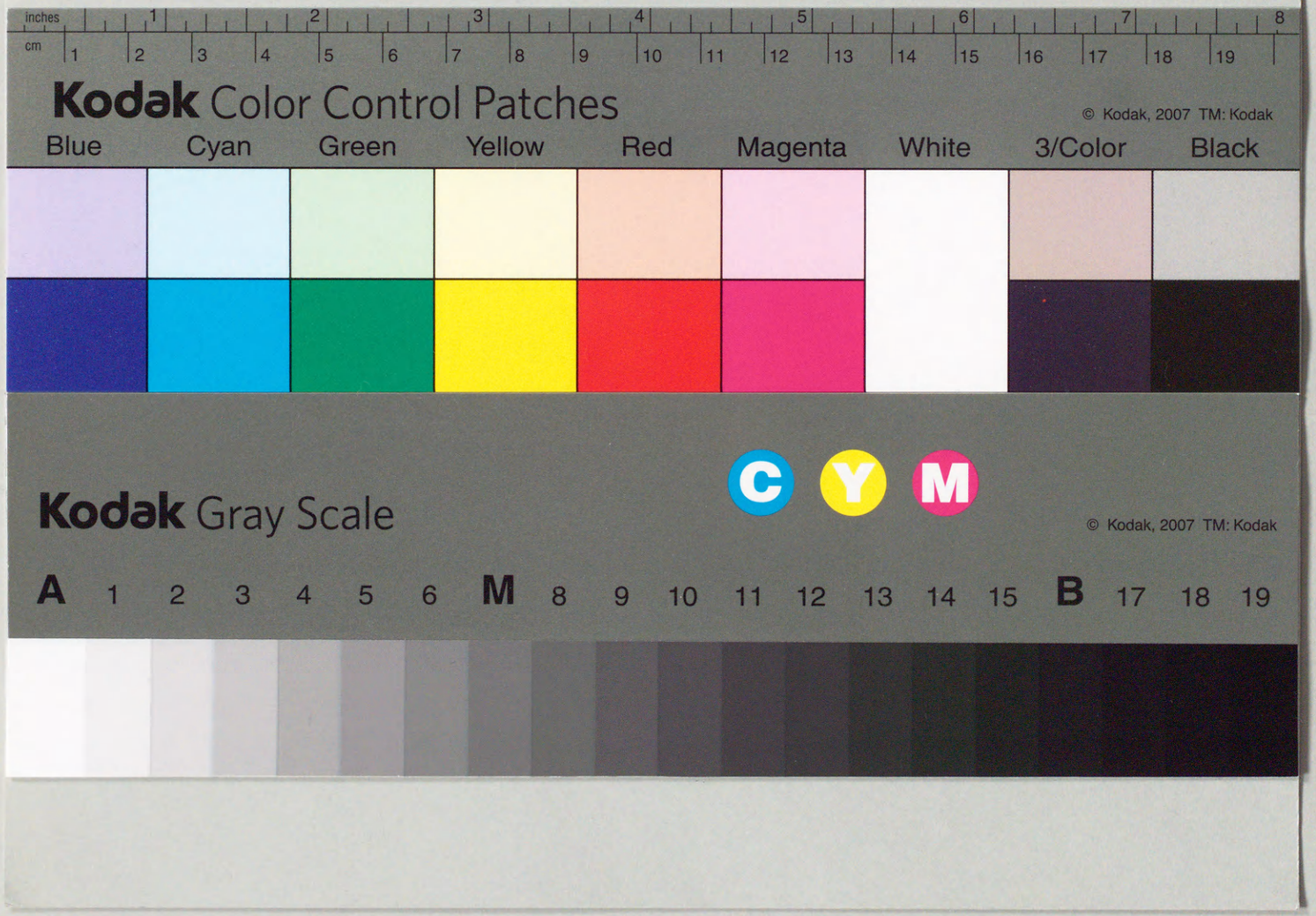

HR100
HR140
HR180
CBF 100%
CBF 50%
CBF 25%
△ LVEDP (mmHg)
p<0.05
P<0.05
LV volume (ml)
LV volume (ml)
LV volume (ml)

Figure 6


● without vibration
○ with vibration
left ventricular chamber stiffness constant K (ml^{-1})
8
7
6
5
0
1
2
3
4
5
6
7
diastolic interval / time constant T


inches
cm
Kodak Color Control Patches
© Kodak, 2007 TM: Kodak
Blue
Cyan
Green
Yellow
Red
Magenta
White
3/Color
Black
Kodak Gray Scale
C
Y
M
© Kodak, 2007 TM: Kodak
A 1 2 3 4 5 6 M 8 9 10 11 12 13 14 15 B 17 18 19